REMARKS

Upon amendment, Claims 1-21 are pending in this application. Claims 14, 16 and 18 have been amended to delete the term "and/or prevention" and to more clearly define the claimed subject matter. Support for this amendment can be found throughout the specification. No new matter has been added by this amendment.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is in condition for allowance.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 14-21 are rejected under 35 U.S.C. §112, First Paragraph, as allegedly failing to comply with the written description requirement, particularly with respect to the nexus of modulation of the vanilloid receptor and a useful treatment of disease. Applicants respectfully disagree and traverse.

Claims 14-21 are also rejected under 35 U.S.C. §112, First Paragraph, as allegedly failing to comply with the enablement requirement, particularly with respect to the prevention of disease. Although Applicants disagree with the Examiner's allegation that the specification is viewed as lacking enablement for prevention of any of the diseases recited, the pending claims have been amended to delete the term "and/or prevention" solely to expedite the prosecution of the present application, and without prejudice to Applicants' right to pursue them in one or more continuation, divisional or continuation-in-part applications.

In view of these amendments and the following discussions, Applicants respectfully submit that the rejection should be withdrawn.

With regard to the methods of treatment of the present claims, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *U.S. v. Telectronics, Inc.,* 857 F.2d 778, 785 (Fed. Cir. 1988). The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *Manual of Patent Examining Procedure* ("MPEP") § 2164.04 (citing *In re Wright,* 999 F.2d 1557, 1562 (Fed. Cir. 1993)).

Accordingly:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those

> used in describing and defining the subject matter sought to be patented *must be taken as being in compliance with the enablement requirement* ... unless there is a *reason to doubt the objective truth of the statements* contained therein which must be relied on for enabling support
>
> * * *
>
> It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Id. (emphases added).

Applicants respectfully submit that whether or not the scope of a claim is broad is irrelevant to the assessment of the enablement of the claim. The question is whether those skilled in the art would have been able to make and use the claimed invention based on the disclosure. *(See U.S. v. Telectronics, Inc.,* at 785).

Applicants respectfully submit that the pending claims are enabled because the specification "contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented." *Id.*

For example, the specification teaches that the compounds of the present invention are useful in that they "show excellent VR1 antagonistic activity " (Page 16, line 28). As such, the compounds are "suitable especially for the ... treatment of diseases associated with VR1 activity, in particular for the treatment of urological diseases or disorders, such as detusor overactivity (overactive bladder), urinary

incontinence, neurogenic detusor overactivity (detusor hyperflexia), idiopathic detusor overactivity (detusor instability), benign prostatic hyperplasia and lower urinary tract symptoms." (Page 16, line 30 – Page 17, line 4). The compounds are also "effective for treating...chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, nerve injury, ischaemia, neurodegeneration, stroke...asthma and COPD since the diseases also relate to VR1 activity." (Page 17, lines 5-10). Other diseases the compounds are useful for the treatment of are described on Page 17, lines 11-26.

Similarly, it is disclosed that the claimed compounds can be prepared by synthetic procedures described throughout the examples (Pages 19-29). Finally, the specification discloses various assays which can be readily performed by one of ordinary skill in the art to determine the desired activity without undue experimentation (Pages 33-41, for example, assays for overactive bladder, persistent pain, acute pain, neuropathic pain, inflammatory pain, diabetic neuropathic pain).

In view of the foregoing, it is clear that sufficient guidance is provided in the specification to allow those of ordinary skill in the art to make and use the claimed invention. Indeed, the claimed invention is directed to the use of obtainable compounds. The skilled artisan can readily determine the activity for any of the compounds encompassed by the claims by using the assays described in the specification, which can be readily used to determine that a synthesized compound is useful in the treatment of the diseases recited in the claims. Moreover, the determination by a physician as to whether a claimed compound is effective in treating a recited disease in a given patient is a type of determination that is always made by physicians for every pharmaceutical. Indeed, the determination is a routine one that every physician is prepared to make, and which requires little or no effort. Therefore, Applicants respectfully submit that one reasonably skilled in the art could make or use the invention as claimed without undue experimentation.

In sum, Applicants respectfully submit that: (1) the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention; (2) the Examiner did not provide any factual or legal basis to doubt that the claims are enabled; and (3) to the extent any experimentation is necessary, such experimentation is not undue.

Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 112, First Paragraph be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 1-21 are rejected under 35 U.S.C. §103(a) as being obvious over United States Patent No. 6,984,647 to Dax et al. ("Dax").

Specifically, the Examiner contends that Dax teaches a Markush of compounds similar to those of Claim 1. Applicants respectfully disagree.

To properly determine a prima facie case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." *Id.* Four factual inquiries must be made: first, a determination of the scope and contents of the prior art; second, a determination of the differences between the prior art and the claims in issue; third, a determination of level of ordinary skill in the pertinent art; and fourth, an evaluation of evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the

resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

The Examiner states that Dax teaches compounds wherein "R3 is the equivalent to the instant tetrahydroquinoline ring." The Examiner points out exemplary compounds in column 52 of Dax.

Applicants respectfully note that the Example shown in the office action (and in column 52 of Dax) is not a tetrahydroquinoline ring but instead an isoquinoline ring. Indeed, none of the compounds disclosed by Dax teach a tetrahydroquinoline ring. Furthermore, tetrahydroquinoline is not disclosed even in the definitions for any of the substituents in the broadest recitation of the Markush group.

One of ordinary skill in the art would expect significantly different chemical properties (steric, electrochemical, pharmacological, etc) between a compound with a tetrahydroquinoline ring system and a compound with an isoquinoline ring system. Indeed, isoquinoline is a fully aromatic ring system whereas tetrahydroquinoline is only partially aromatic. Applicants note that all of the ring systems disclosed in the examples of Dax are fully aromatic (phenyl, thienyl, naphthylene, pyridine, quinazoline, or quinoline). Similarly, the aromatic isoquinoline ring would be expected to be planar in three dimensional space; whereas, the nonaromatic portion of tetrahydroquinoline would be expected to be non-planar. One or ordinary skill in the art would recognize that such conformational differences, at a minimum, could dramatically affect the ability of the compounds to modulate the same receptors pharmacologically.

As such, Applicants respectfully assert that one of ordinary skill in the art, at the time of the invention, would have lacked the motivation to modify the fully aromatic isoquinoline ring with the mixed methylene / aromatic ring of the instant tetrahydroquinoline derivatives without potentially sacrificing the purported properties of the compounds. Indeed, even if one were to have modified the compounds taught by Dax, there would have been no expectation of success in maintaining the desired properties of the compounds.

Accordingly, Applicants respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. § 103

CONCLUSION

In view of the amendments and remarks made herein, Applicant submits that the application is in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. If a telephone conference with Applicant's representative would be helpful in expediting prosecution of the application, Applicant invites the Examiner to contact the undersigned at the telephone number indicated below.

Applicants believe that no additional fees are required for consideration and entry of this paper. However, Applicants authorize the Director to charge any required fee or credit any overpayment to Deposit Account No. 04-1105, under Order No. 82819(303989).

Dated: December 23, 2008

Respectfully submitted,
Electronic signature:
/Nicholas J. DiCeglie, Jr./
Nicholas J. DiCeglie, Jr.
Registration No.: 51,615
EDWARDS ANGELL
PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(212) 308-4411
Attorneys/Agents For Applicant
Customer No. 35969